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The specification has been amended editorially and to correct those errors noted by the examiner. The claims have been rewritten to more particularly define the invention in a patentable manner over the prior art. The applicant kindly thanks the Examiner for the suggestions.

Claims rejection 35 USC 112

Claims 1-7 are rejected in the OA as failing to define the invention in the manner required by 35 U.S.C. 112, second paragraph. The applicant has rewritten the claims to comply with 35 112. Accordingly, the applicant submits that the new claims as written do comply with 112, second paragraph, and therefore kindly requests withdrawal of this objection.

Claims rejection 35 USC 102

Claims 1-5 and 7 are rejected in the OA as being anticipated by the article DUNNE et al, British Journal of Pharmacology, 1998, 125, 225-233. Applicant respectfully acknowledges receipt of the article and applicant acknowledges as well the first reported biological activity of the (R,S)-S-adenosyl-l-methionine as reported in this paper. The applicant however argues the potential nocive side effects of this particular diasterioisomer of SAM-e in light of its reported ability to bind to transferase enzymatic sites and **not participate in the most fundamental of the known activities of this molecule, namely methylation and transulferation.** Applicant furnishes the Examiner in an accompanying IDS with two papers cited in the specifications of this present patent application but which were not supplied to the Examiner prior to this first OA. The applicant begs the Examiner's indulgence for this oversight.

In the first paper, by Borchardt and Wu entitled "Potential Inhibitors of S-adenosylmethionine-dependent methyltransferases. 5. Role of the Asymmetric Sulfonium Pole in the Enzymatic Binding of Ad-

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enosyl-L-methionine", Journal of Medicinal Chemistry, 1976, Vol. 19, No. 9, pp 1099-1103, the authors report that the (+)-SAM (no longer used nomenclature for (R,S)-S-adenosyl-l-methionine is a potent inhibitor of enzyme-catalyzed transmethylation reactions. See Conclusions, p. 1102, paragraphs 1 and 2. Interestingly, however, (+)-SAM binds to the site but does not participate in the transulferation or methylation reactions. The applicant views this fact to be important in the argument for as enriched a concentration of (S,S)-S-adenosyl-l-methionine in any pharmaceutical composition as possible for the following reasons:

-methylation reactions control gene expression

-hypomethylation of DNA leads to cancer expression

In the second paper included in this amendment, Segal and Eichler, Archives of Biochemistry and Biophysics, Vol 275, No. 2, December, pp 334-343, 1989, "The Specificity of Interaction between S-Adenosyl-l-methionine and a Nucleolar 2-0-Methyltransferase" point out the importance of the chirality of the sulfonium center for methyltransferase activities. They report that (S,S)-S-adenosyl-l-methionine has a 10 fold higher binding affinity as compared to the (R,S)-S-adenosyl-l-methionine. (See page 341, second column.)

In another paper (Detich et al "The methyl donor S-adenosylmethionine inhibits active demethylation of DNA; a candidate novel mechanism for the pharmacological effects of S-adenosylmethionine." J Biol Chem. 2003 Jun 6;278(23):20812-20). This paper is included in this amendment in the IDS and is pertinent to the current argument for the importance of the preferred (S,S)-S-adenosyl-l-methionine enrichment concept of the patent application. The authors point out the tumor protective mechanism of SAM-e and the importance of intracellular SAM-e concentrations in cancer prevention. Presumably this is due to the ability of SAM-e to prevent DNA hypomethylation. Indeed, DNA hypomethylation is a hallmark of cancer cells and the correction of this hypomethylation leads to proper gene expression and reversal or prevention of cancer. However, in light of the known inability of (R,S)-S-adenosyl-l-

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methionine to participate in methylation or transulfuration reactions (indeed, it inhibits these reactions), it becomes increasingly apparent that SAM-e compositions should contain the least amount of (R,S)-S-adenosyl-l-methionine possible.

The applicant respectfully points out that although DUNNE teaches that (S,S)-S-adenosyl-l-methionine and (R,S)-S-adenosyl-l-methionine have different biological effects in the invitro assay that is used, the group did not attribute the effects necessarily to the known mechanism of action of SAM-e, that is, methylation and transulfuration. In fact, they pointed out that it was possible that the actions of SAM-e might have been due not to the SAM-e itself but to breakdown products such as adenosine or methylthioadenosine. (See DUNNE et al p. 231 column one, paragraph 2.) DUNNE et al however did not point out the potential nocive effects of (R,S)-adenosyl-l-methionine. They did discuss on page 231, column two, paragraph 2 towards the bottom of the paragraph that the (R,S) SAM-e racemer was excluded from the transmethylation and trans sulfuration reactions due to steric considerations. This in itself should be a sufficient warning to all not to use this particular racemer in clinic. However, they gave no caution or warning against such use.

The applicant acknowledges that DUNNE et al teach the use of (R,S)-adenosyl-l-methionine1,4 butanedisulphonate salt as well as (S,S)-adenosyl-l-methionine 1,4 butanedisulphonate salt. However, the applicant again wishes to respectfully point out that DUNNE et al did not caution against the use of the (R,S)-adenosyl-l-methionine1,4 butanedisulphonate salt in clinic due to its ability to inhibit transmethylation as well as transulfuration reactions. They did not view this as important. Indeed, to this day, very few researchers besides the applicant have pointed out the potential dangers in the clinical use of compositions of SAM-e with high concentrations of (R,S)-adenosyl-l-methionine.

The applicant has rewritten the claims to comply with 35 102. Accordingly, the applicant submits that the new claims as written do comply with 102, and therefore kindly requests withdrawal of this objection.

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Claims rejection 35 USC 103

Claims 1 and 6 are rejected in the OA as being unpatentable over the article DUNNE in view of the article MATOS et al., Bio-organic Chemistry, 1987, 15, 71-80. The applicant kindly refers the Examiner to the above argument re DUNNE and to the following argument regarding MATOS. The applicant also kindly thanks the Examiner for the furnished paper by MATOS dealing with the effect of counterions on the stability of S-adenosyl-l-methionine to epimerization. However, MATOS deals with issues of stability of SAM-e in solution and its relative stability in terms of rate of epimerization in solution. It is now known that SAM-e as it is commercially produced and sold abroad and in the US is unstable to epimerization on the shelf (i.e. as a powder) at ambient temperature.

In a recent paper by Cannon et al entitled "A stereospecific colorimetric assay for (S,S)-adenosylmethionine quantification based on thiopurine methyltransferase-catalyzed thiol methylation." Analytical Biochemistry, 308, (2002) 358–363, the authors have proven that commercially available SAM-e tosylate is unstable to racemization over time. (See page 362 column one paragraph 2.) This is, of course, different from what MATOS teaches since MATOS does not deal with SAM-e as a powder but in solution. Consequently, the applicant kindly points out that MATOS' discussions of SAM-e racemic stability will not have bearing on the discussion of SAM-e in the powder form. In fact, Cannon et al point out on page 362 column one paragraph 2 that the SAM-e that they analyzed contained roughly 50% (S,S)-adenosyl-l-methionine.

In commercial SAM-e available in the US at the time of the analysis of Cannon et al and up to today as well, the SAM-e is normally thought to contain 80% (S,S)-adenosylmethionine: 20% (R,S)-adenosylmethionine. The change from 80%-50% in concentration of (S,S)-adenosylmethionine to (R,S)-adenosylmethionine represents an important deterioration of the SAM-e over time. At the time of the applicant's patent application, this information was not available. However, the applicant understood the impor-

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tance of having the highest concentration of (S,S)-adenosylmethionine available in a SAM-e product to overcome what appeared at the time to the applicant to be the inevitable problem of unstoppable epimerization of (S,S)-adenosylmethionine to (R,S)-adenosylmethionine at room temperature over time. The applicant argues against high concentrations of (R,S)-S-adenosyl-l-methionine in any composition since this enantiomer potentially could interfere with DNA methylation, could block transulfuration reactions, and could have clinically adverse effects.

In the intervening time of the applicant's patent application, Berna et al had a patent application published that also discussed the problems associated with racemization of SAM-e. The applicant, in an IDS received in the USPTO on 1.10.2002, informed the patent office of a patent application by Berna et al detailing a process for the production of (S,S)-adenosylmethionine at 97% purity. This patent application has a priority date of May 2000 and it consequently presents a problem of prior art in terms of some of the claims of this present application. They had solved to some extent the problem of SAM-e racemization over time by providing for a manufacturing process that allowed for a 97% (S,S)-adenosyl-l-methionine concentration and a 3% (R,S)-adenosylmethionine concentration. However, Berna et al did not realize apparently that the 97 % (S,S)-adenosyl-l-methionine concentration would decline overtime at room temperature. If they had realized this, they too would have attempted to call out in their patent application the concentrations of (S,S)-adenosyl-l-methionine to about 80%. However, they did not do so since they thought the SAM-e would be stable. In light of the Cannon paper, it is obvious that SAM-e is not stable to racemization at room temperature.

Ideally, one can mitigate the rate of SAM-e racemization at room temperature on the shelf by increasing or enriching the amount of (S,S)-adenosyl-l-methionine in the composition. To date, no one has conceived of this except the applicant. The applicant submits that this is novel, new and unexpected. If someone would have thought of it before, they surely would have done it by now.

The applicant has rewritten the claims and has presented arguments to comply with 35 103. Accord-

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ingly, the applicant submits that the new claims as written do comply with 103 and therefore kindly requests withdrawal of this objection.

By the above amendment, the applicant has rewritten all the claims to define the invention more particularly and distinctly so as to overcome the rejections and define the invention patentably over the prior art. Therefore it is submitted that patentable subject matter is clearly present. If the examiner agrees but does not feel that the newly written claims as submitted in this amendment are technically adequate, applicant respectfully requests that the examiner write acceptable claims pursuant to MPEP 707.07 (j).

Conclusion:

For all the reasons given above, applicant respectfully submits that the new claims of this present amendment comply with Section 112, the claims define over the prior art under Section 102 and the claimed distinctions are of patentable merit under Section 103 because of the information provided. Accordingly, applicant submits that this application is now in full condition for allowance, which action applicant respectfully solicits.

Applicant kindly thanks Examiner for suggestions.

Very respectfully,

Rolland Hebert

Rolland Hebert, Applicant Pro Se

427 Bellevue Ave. E. Suite 301

Seattle, WA 98102

Cell phone 206.650.4489

Customer number 29133